510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:
k042494

B. Purpose for Submission:
New device

C. Analyte:
Complement 3 (C3) and Complement 4 (C4)

D. Type of Test:
Quantitative, immunoturbidimetric.

E. Applicant:
Ortho-Clinical Diagnostics, Inc.

F. Proprietary and Established Names:
VITROS Chemistry Products Complement 3 and Complement 4 Reagents
VITROS Chemistry Products Calibrator Kit 20
VITROS Chemistry Products FS Calibrator
VITROS Chemistry Products Protein Performance Verifiers I, II and III

G. Regulatory Information:

1. Regulation section:
   21 CFR § 866.5240, Complement Components Immunological Test System
   21CFR § 862.1150, Calibrator
   21 CFR § 862.1660, Quality control material (assayed and unassayed)

2. Classification:
   Class II, C3 and C4 reagents and calibrator
   Class I, Quality control material

3. Product Code:
   CZW, C3
   DBI, C4
   JIT, Calibrator, secondary
   JJX, Single (specified) analyte controls (assayed and unassayed)

4. Panel:
   Immunology (82)

H. Intended Use:

1. Intended Use
   VITROS Chemistry Products C3 and C4 reagents are used to quantitatively measure C3 and C4 concentration in human serum and plasma. Measurements of these proteins aids in the diagnosis of immunologic disorders, especially those associated with deficiencies of complement components.

   VITROS Calibrator kit 20 is used to calibrate VITROS 5,1 FS Chemistry System for quantitative measurement of transferrin, C3, C4, IgA and IgM (multianalytes).

   VITROS Chemistry Products Protein Performance Verifiers I, II and III are assayed controls used to monitor the performance of Transferrin, C3, C4, IgA and IgM Reagents on the FS 5,1 Chemistry Systems.

2. Indication(s) for use:
   As an aid in the diagnosis of immunologic disorders associated with complement components.

3. Special condition for use statement(s):
   The devices are for prescription use only.

4. Special instrument Requirements:
   VITROS 5,1 FS Chemistry System (k031924).

I. Device Description:

The VITROS Chemistry Products C 3 and C 4 devices consist of thin film, dry products coated on polyester supports. C3 reagent is a dual chambered package containing ready to use reagents 1 and 2. Ingredients of the reagents contain buffer, polymer, inorganic salt and goat anti-serum.

The VITROS Chemistry Products Calibrator kit 20 contains 5 levels for the calibration of Vitros 5,1 FS Chemistry Systems for the quantitative measurement of C3and C4. The calibrator kit is prepared from processed human serum to which inorganic salts, buffers and preservatives have been added.

Protein performance verifiers contain 3 levels of assayed controls (low, medium and high) for use in monitoring performance of C3 and C4 on VITROS Chemistry 5,1 FS Systems. Protein performance verifiers are prepared from processed serum to which inorganic salts buffers and preservatives are added. For C3 nominal value used – concentration for level I is 64 mg/dL, level II is 127 mg/dL and level III is 256 mg/dL. For C4 nominal value concentration for level I is 13 mg/dL, level II is 25 mg/dL and level III is 49 mg/dL.

J. Substantial Equivalence Information:

1. Predicate device name(s):
   Beckman IMMAGE C3 assay, Dade Behring C4 assay and VITROS Performance verifiers.

2. Predicate K number(s):
   Beckman IMMAGE C3 (k964842). Dade Behring C4 (k860894) and VITROS Performance verifiers (k041720, k955134)

3. Comparison with predicate:

DEVICE	PREDICATE
A. Similarities	
Intended Use. Used to quantitatively measure C3 and C4 concentration in human serum and plasma. Measurements of these proteins aids in the diagnosis of immunologic disorders, especially those associated with deficiencies of complement components.	Same
Assay Format – Quantitative	Same
Performance Verifiers – assayed controls for monitoring performance of transferrin, C3, C4, IgA, IgG and IgM reagents	Same
B. Differences	
Assay type – Immunoturbidimetric	Rate nephelometric
Instrument - VITROS 5,1 FS Chemistry Systems	Beckman IMMAGE and Dade Behring nephelometer
Sample Type – Serum and plasma	Serum
Control levels – low, medium and high	Low and high

K. Standard/Guidance Document Referenced (if applicable):
NCCLS Guide line EP5-A, EP-7A, EP -9A, C28.

L. Test Principle:
Immunoturbidimetric method.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:
   a. *Precision/Reproducibility:*
   Within-day and within laboratory precision - Two runs were performed on each of 22 days on the VITROS 5,1FS System. Each run included 3 evaluation samples (two control sera and one calibrator) were assayed in duplicate. In addition, one set of the five

level calibrators was run once weekly. The calibrator samples tested each week were used to generate a calibration curve for determining results for that week. Runs within the day were separated by at least two hours. Within day precision was determined using two runs per day with two replications per run. Within lab precision was determined using a single lot of reagents and calibrating weekly. The results of the test samples for each matrix were analyzed using NCCLS EP- 5A Guideline.

C3 reagent (mg/dL)			%CV (mean)	#observed	#days
Mean Conc	Within Day (SD)	Within Lab (SD)			
74	0.7	1.6	2.2	88	22
142	2.1	4.5	1.415	88	22
292	9.6	13.7	2.917	87	22

C4 reagent (mg/dL)			%CV (mean)	#observed	#days
Mean Conc	Within Day (SD)	Within Lab (SD)			
13.4	0.18	0.27	2.0	87	22
25.6	0.16	0.43	1.7	87	22
45.1	0.37	0.69	1.15	88	22

b. Linearity/assay reportable range:

Evaluation of the linearity of the VITROS C3 Reagent assay and comparison of the measured with calculated analyte concentration of mixed pools, prepared at concentrations covering the range of the assay were performed based on NCCLS EP6-A. The high pool had a concentration of 381 mg/dL and the low pool had a concentration of 39.7 mg/dL. Thirteen levels spanning the assay reportable range of admixtures of the high and low pools were created. Three determinations of each level were made together with the Protein Verifiers. Analysis by linear regression indicated that the assay is linear across the range tested. $Y = 3.359x + 40.789$, $R^2 = 0.9986$. The product claim for linearity over reportable range is 40 to 380 mg/dL.

For the C4 assay, the high pool was the high calibrator level with a concentration of 72. 7 mg/dL and the low pool was the low level calibrator with a concentration of 7.5 mg/dL. Thirteen levels spanning the assay reportable range of admixtures of the high and low pools were created and three determinations of each level assayed. Linear regression plot showed $–y = 0.6663 x + 7.5846$, $R^2 = 0.9994$. The C4 assay is linear across the range tested (7.5 to 72.7 mg/dL). The product claim for linearity over the reportable range is 8.0 to 60 mg/dL.

Dilution Study - A total of 5 patient samples, one high calibrator and one concentrated patient pool at the high end of the assay range were evaluated. Recoveries were calculated based on undiluted values measured on the same samples run on the VITROS 5,1 FS Chemistry System using C3 reagent. Recovery of each sample was determined as % of the neat sample concentration (% recovery =diluted sample result x100, divided by neat concentration of sample). The two lots tested showed the mean recovery value as 100.1% with individual sample recovery range of 97.1% to 105.9% (acceptance criteria was set at 89.6%-110.4%). Samples with values greater than the reportable range (40-380 mg/dL) may be diluted up to 1 part sample with 1 part diluent (saline).

In the case of C4 assay, a total of 5 patient samples, one high calibrator and one concentrated patient pool at the top of assay range were evaluated. Recoveries were calculated based on undiluted values measured on the same samples using VITROS 5,1FS Chemistry system and C4 reagent. Mean percentage recovery value was 98.9% with an individual sample recovery range of 90.4% to 105.4%. All samples passed acceptance criteria 90.1% - 109.9%. Samples with values greater than the reportable range (8.0-60.0 mg/dL) may be diluted 1:1 ratio with diluent.

c. *Traceability (controls, calibrators, or method):*
Values assigned to the Calibrator Kit 20 for complements C3 and C4 are traceable to IRMM /IFCC (Institute for Reference Methods and materials) CRM 470 reference material.

Calibrator Value assignment for C3 and C4 - a five level set of calibrators are prepared using 5,1FS Chemistry System on-analyzer dilution of CRM 470. The calibration standards are used to measure and assign a master lot of working calibrators.

d. *Detection limit (functional sensitivity):*
No provided.

e. *Analytical specificity:*
Interfering substances were tested with C3 reagent at C3 concentration of approximately 97 mg/dL according to NCCLS EP-7A. Hemoglobin (1000 mg/dL) and bilirubin (60 mg/dL) interference were tested at concentrations of approximately 70mg/dL and were found not to interfere with a bias <9 mg/dL.

Acetominophen (200 µg/mL), Amoxicillin(20 µg/mL), lidocaine (60 µg/mL), theophylline (250 µg/mL), salicylic acid (500 µg/mL) etc. were tested and bias<7 mg/L at the specified concentrations.

Results showed that patient samples containing high levels of IgG can result in a bias greater than the acceptance limit.

f. Assay cut-off:
Not provided.

2. Comparison studies:

a. Method comparison with predicate device:
A total of 140 serum samples were assayed using VITROS C3 assay and the Beckman IMMAGE C3 assay for comparison. Testing of individual samples with both the methods was performed within 3 days. All samples were analyzed in triplicate. Data were screened for outliers according to NCCLS EP9-A. Two reagent lots were used for testing. Least squares linear regression analysis showed (VITROS) =0.95x (IMMAGE) + 11 (mg/dL) with a correlation coefficient of 0.98.

For C4 assay, 143 serum samples were assayed using VITROS C4 assay and Dade Behring's C4 assay (Prospec) on the same day. Two reagent lots were used. Data were screened for outliers using NCCLS EP5-A and only data within the reportable range were analyzed. Linear regression analysis showed (VITROS) = 0.93 x (Prospec) + 3.0 (mg/dL) with a correlation coefficient of 0.976.

b. Matrix comparison:
Fresh blood was drawn into multiple collection tubes from 6 individuals. An additional 60 samples were collected in serum and lithium heparin tubes for serum and plasma comparison. Serum and plasma separator tubes were used and separated with in 1 hour of collection. NCCLS EP-5A was used for calculation of individual results. The results were within acceptable limits except for EDTA with a mean bias of -11% which is outside the acceptance criteria. EDTA plasma is not recommended for the C3 assay.

The number of samples tested for C4 was the same as for C3. Serum and plasma results were within the acceptance criteria and the recommendation is –serum, heparin plasma and EDTA plasma should be used.

3. Clinical studies:

a. Clinical sensitivity:
Not provided.

b. Clinical specificity:
Not provided.

c. Other clinical supportive data (when a and b are not applicable):
Not applicable.

4. Clinical cut-off:
Not provided.

5. Expected values/Reference range:
The expected values for C3 were determined by assaying 122 samples from healthy subjects using 2 reagent lots. The results obtained were 88.6 to 167 mg/dL. The 90% confidence intervals of the 2.5 and 97.5 percentile values were 84.6 to 96.5 mg/dL and 158 to 203mg/dL respectively. The evaluation was performed using NCCLS C28 guideline. The reference interval based on the two lots was determined to be 87.7 to 165mg/dL.

The expected values for C4 were determined by testing 122 samples from healthy subjects using 2 lots of C4 assay reagents and evaluation was performed according to NCCLS guideline C28. Reference interval for lot 1 was 13.1 to 45 1mg/dL. The 90 % confidence intervals of the 2.5 and 97.5 percentile values were 7.67 to 17.0mg/dL and 41.0 to 59.7mg/dL respectively. Reference interval for lot 2 was 14.2 to 42.7mg/dL. The 95% confidence intervals for the 2.5 and 97.5 percentile values were 7.98 to 56.3 mg/dL. Overall reference interval was determined to be 13.7to 43.9mg/dL for the normal population.

N. Conclusion:
The submitted information in this premarket notification is complete and supports a substantial equivalence decision.